b.) Remarks

Claim 71 is added in order to more particularly recite a preferred embodiment of the present invention, and claims 42-45, 58, 59, 61-63, 65 and 68 are amended for better idiomat usage or dependency. The subject matter of the amendment is found at specification page 24, lines 5-10.

Previously, Applicants amended their claims to recite the phrases "without destroying said granule bearing a coating film" (in claims 42 and 63) and "without destroying the granule" (in claims 44 and 64). That language was deleted without comment in a preliminary amendment in order to expedite prosecution following rejection under 35 U.S.C. §112, first paragraph, in the September 13, 2004 Final Office Action.

Nonetheless, Applicants are, as explained below, relying on these unexpected features in part to negate any possible *prima facie* obviousness. An applicant can rebut a *prima facie* case of obviousness by prosecuting comparative test data showing that the claimed invention possesses unexpectedly improved properties that the prior art does not. *In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987).

The claims have not been amended to re-present these features, however, since there is no requirement that the claims must recite the unexpected advantage. However, from the following, it is clear that the improvement achieved by the present

invention not only flows directly from the instant specification[1] (*In re Chu*, 66 F.3d 292 (Fed. Cir. 1995); *In re Zenitz*, 333 F.2d 924 (CCPA 1964); *In re Khelghatian*, 314 F.2d 870 (CCPA 1966)), it is explicitly taught in the specification as filed.[2]

Claims 42-70 are rejected under 35 U.S.C. §103(a) as being obvious over Moriomoto (EP 0 650 826) in view of Roche (U.S. Patent No. 5,075,114). Claims 42-70 are also rejected as being obvious over Tsushima (U.S. Patent No. 6,036,974) in view of Roche.

This rejection is respectfully traversed. Prior to setting forth their bases for traversal, however, Applicants would like first to briefly discuss the salient features of the present invention and, *inter alia*, its patentable nature over the prior art.

---

[1] As discussed at page 14, lines 5 et seq.,

> "[w]hen a tablet including granule having film on the surface is produced, the film isn't destroyed.
>
> Also, when a tablet including granule containing active substance in a base matrix is produced, the function of the contained matrix isn't damaged."

Applicants respectfully submit those of ordinary skill readily appreciate from page 14 that the granules are not destroyed in a process of mechanical compression using a punch and die that affects the entire tablet (as opposed, for instance, to abrasive or chemical processes which can affect the coating film only) since, if the coating film is not damaged, the granule is necessarily not damaged, as well. Similarly, when the "function" of the matrix in the granule is not damaged, it is well-understood that the granule too is itself undamaged. Nonetheless, if it will assist the Examiner's consideration, Applicants will be happy to submit a Declaration under Rule 132 evidencing that the granules are not destroyed, upon receipt of a request therefore, in conformity with *In re Reynolds*, 443 F.2d 384 (CCPA 1971); *In re Smythe* 480 F.2d 1376 (CCPA 1973). See MPEP 2163.07(a).

[2] > [Applicants] have taught that a tablet including granule can be produced by this method without damaging the coated film of the granule, so called microcapsule, damaging the contained granule, nor deforming plasticity. After hard endeavor, they have completed the present invention. (Emphasis added.)

Specification page 16, lines 15-20.

As the Examiner is aware, the present invention relates to methods of producing tablets which maintain granule integrity, and tablets produced thereby. As recited in the pending claims, the method is characterized in part that a tablet is produced from a molding material comprising granules. (See claim 42, line 3, claim 44, line 3, etc.) The molding material contains no lubricant (see claim 42, line 6, claim 41, line 6, etc.) and is compressed using lubricated punches and die, wherein the lubricant is provided (i) only on surfaces of the die and punches and (ii) in an amount of from 0.0001 to 0.2 weight percent/tablet. (See claim 42, lines 11-13, claim 44, lines 11-12, etc.)

These features, at least, are not taught or suggested by Morimoto or Tsushima, whether or not taken in view of Roche.

Those of ordinary skill understand that to obtain sufficiently hard tablets a high tabletting pressure is required (1-2 ton/cm^2). See specification page 6, lines 8-10. However, these forces destroy the granule and alter the release rate intended by the formulation. Specification page 6, lines 10-19. That is, when a molding material containing granules (of coated active substance or active substance in a base matrix) is compressed to produce a tablet, the structure of granules is generally destroyed by the tabletting pressure. Thus, the function of the granules is damaged. Of course, to prevent destruction of the granule structure and damage of their function, a tablet could be compressed at a low tabletting pressure. However, it has been thought that when low tabletting pressure is used, only tablets of inferior hardness are obtained.

Internal lubricants are utilized for a variety of reasons, including lowering the required tabletting pressure. That is to say, it is understood that even higher tabletting pressures are required when internal lubricant is omitted. Thus, internal lubricant is

particularly necessary when pressing coated granules, or granules of active agent in a matrix, as in the present invention.

However, Applicants have unexpectedly learned that when no internal lubricant is provided (e.g., when the molding material contains no lubricant), coated granules and granules of active agent in matrix can be tabletted at pressures that do not to damage the granules while still obtaining an acceptable hardness, by lubricating the punches and die in amounts of no more than 0.2 weight percent/tablet.

Accordingly, by operation of the present invention, a superior tablet with intact granules, e.g., a durable tablet that does not have diminished sustained release function or enteric property, etc., can be produced. Such improved properties are well-established by the comparative test results and experiments in the specification of the present invention, as will be discussed below.

Morimoto discloses a tabletting machine in which sprayed lubricant is uniformly applied on the surface of a tablet. The tabletted material is powdered or granular pharmacological agent. However, Morimoto does not disclose tabletting Applicants' granules in which active substance is coated with film (claims 42 and 63) or granules including active substance in a base matrix (claims 44 and 64). Further, although Morimoto discloses that applying lubricant on the tablet surface prevents sticking during tabletting, Morimoto does not disclose or suggest that those particular granules would not be damaged.

These deficiencies are not overcome by Roche, which teaches tabletted particles coated with polymer blend for taste masking the active substance and/or providing sustained release of the active substance. Roche teaches selecting a specific

coating material component which is not damaged under pressure so as to avoid damaging the function of the granule.

The Examiner says that it is obvious for a person skilled in the art to substitute the pharmaceutical granules of Roche for the pharmaceutical material of Morimoto.

However, even if Morimoto and Roche are combined, there is no teaching or suggestion to exclude lubricant from the molding material. Accordingly, there is no *prima facie* obviousness. More importantly, there is no suggestion or expectation that, when tabletting granules including coated active substance, or active substance in a base matrix, with lubricant is applied only on the die and punch surfaces, a sufficiently hard tablet can be obtained without destroying the granule. Therefore, even assuming *arguendo* that a *prima facie* obviousness is established, such is necessarily overcome and the amended claims are unobvious over the prior art.

Tables I and II (attached at Tab A) show the composition of the tablets produced in experiments 3 and 4, described from specification page 62, line 5 to page 64, line 19. Table 1 utilizes sustained release microcapsules (see page 60, line 17 to page 61, line 14) and Table 2 utilizes enteric coated microcapsules, (see page 61, line 15 to page 62, line 3).

Hardness

These microcapsules are prepared both (i) using an internal lubricant (1.0 wt% magnesium stearate) as in Morimoto and (ii) without any internal lubricant but with

surface-applied lubricant only, as in the pending claims. These materials were tabletted at 500, 1000 and 1500 kg/punch and hardnesses were evaluated.

As shown in Table 3, the tablet of the present invention (in which lubricant is not contained in a molding material and is applied only on the surface thereof) has superior hardness (5.0 and 5.5 for experiments 3 and 4, respectively) even when it is tabletted at pressures as low as 500kg. This hardness is markedly superior to the closest prior art tabletted at double the pressure, e.g., 1000 kg (4.5 and 5.0 for comparisons 4 and 5, respectively).

Granule Integrity

Tables IV and V show the result of elution tests using tablets with substantially same hardnesses of 4.5 – 5.5. The tests were conducted to compare the tablets of experiment 5 with comparison 7, and the tablet of experiment 6 with comparison 8.

Table IV provides result of comparing sustained release activities of the tablets from experiment 5 and comparison 7. The granule of reference 1 is shown as a reference. As shown in Table IV, the tablet of the present invention (experiment 5) shows the same sustained release as the granule of reference 1[3], so the tabletting process did not damage the granules. However, in the comparison 7, the release time of active ingredient increases several-fold. Therefore, it is clear that the granules are destroyed in Comparison 7. However, the close relationship between Experiment 5 and Reference 1 indicate that the tablet of experiment 5 is compressed without destroying the contained granules.

---

[3] Reference 1 is an untabletted microcapsule, see page 60, lines 17 et seq.

Similarly, Table V shows the comparison result of sustained release of the tablet in the experiment 6 and the tablet in the comparison 8. The granule in reference 2[4] is also shown as a reference. As evidenced in Table V, the tablet of the present invention (experiment 6) again shows the same enteric ability as the granule in reference 2. However, in comparison 8, the active ingredient is released in the first solution of the Japanese Pharmacopoeia. Therefore, it is understood that the tablet of the experiment 6 is compressed without destroying the contained granule, but the enteric coated granules are destroyed in prior art comparison 8.

The advantages attained by the present invention concerning both hardness and granule integrity is plainly of great utility to those of ordinary skill herein and, moreover, are neither taught nor suggested by the prior art.

Tsushima is less relevant than Morimoto. Tsushima discloses an aqueous tablet. For instance, according to Tsushima, ubidecarenone, mannitol and sucrose fatty acid ester are mixed, then 40ml of ethanol solution containing polyvinylpyrrolidone is slowly added. A mold having a diameter of 10mm and a thickness of 5mm was filled with this mixture. After pressure of 20Kg was exerted, the molded mixture was removed from the mold and dried to obtain a tablet. In Tsushima, it is required to admix 10% by weight ethanol or water to the compression material (see second column, lines 5 – 6).

As before, the Examiner says that it is obvious for a person skilled in the art to modify Tsushima by utilizing the pharmaceutical material of Roche.

However, when 10% by weight ethanol or water is added to Roche's pharmaceutical granules including a coated active substance, the structure of the granule is

---

[4] Reference 2 is an enteric coated microcapsule, see page 61, lines 15 et seq.

immediately destroyed by the ethanol or water. Accordingly, Tsushima and Roche cannot be combined as posited by the Examiner.

Moreover, neither Tsushima nor Roche disclose or suggest that lubricant is applied only on the surface of tablet. Therefore, even if they are combined, they still fail to suggest one additional salient characteristic of the present invention, namely that the molding material contains no lubricant.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 42-71 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

Lawrence S. Perry
Attorney for Applicants
Registration No. 31,865

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200

LSP\ac\nbm

NY_Main 522894_1

Table 1

	experiment 3	comparison 4
granule of reference 1	1000g	1000g
lactose	700g	700g
crystalline cellulose	300g	280g
magnesium stearate (to be mixed with molding material)	0g	20g (1.0% by weight)
magnesium stearate (to be applied on tablet's surface)	0.07 % by weight	0 % by weight

Table 2

	embodiment 4	comparison 5
granule of reference 2	500g	1000g
lactose	350g	700g
crystalline cellulose	150g	280g
magnesium stearate (to be mixed with molding material)	0g	20g (1.0% by weight)
magnesium stearate (to be applied on tablet's surface)	0.03 % by weight	0 % by weight

Table 3 (rewritten from table 3 in specification)

tableting pressure (kg/punch)	tablet hardness			
	experiment 3	comparison 4	experiment 4	comaparison 5
500	5.0 (tablet of experiment 5)	2.0	5.5 (tablet of experiment 6)	2.0
1000	10.0	4.5 (tablet of comparison 7)	11.0	5.0 (tablet of comparison 8)
1500	14.0	9.0	15.0	9.5

table IV (data is rewritten from table 4 in specification)

elution time (hr)	solution	experiment 5	comparison 7	reference 1
0	Japanese Pharmacopoeia first solution	0	0	0
0.25		5	15	5
0.50		12	40	10
0.75		15	65	15
1.00		22	80	20
1.50		30	95	30
2.00		41	100	40
(2.00)	Japanese Pharmacopoeia second solution	41	100	40
2.50		51	100	50
3.00		61	100	60
4.00		82	100	80
5.00		100	100	100

table V (data is rewritten from table 5 in specification)

elution time (hr)	solution	experiment 6	comparison 8	reference 2
0	Japanese Pharmacopoeia first solution	0	0	0
0.25		0	30	0
0.50		0	70	0
0.75		0	95	0
1.00		0	100	0
1.50		0	100	0
2.00		2	100	1
(2.00)	Japanese Pharmacopoeia second solution	2	100	1
2.50		55	100	60
3.00		100	100	100
4.00		100	100	100
5.00		100	100	100